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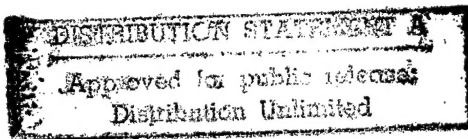
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S. M. Dionesov

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## PAIN. THE EFFECT OF PAIN STIMULI ON THE VITAL ACTIVITY OF THE ORGANISM

[This is a translation of an excerpt from a book by S. M. Dionesov, Doctor of Biological Sciences, entitled Bol; Vliyaniye Bolevykh Razdrazheniy na Zhiznedeystel'nost Organizma (Pain. The Effect of Pain Stimuli on the Vital Activity of the Organism), 1958, pages 191-202.]

### The Role of Pain Stimuli in the Origin of Traumatic Shock

As we can see, pain stimuli cause considerable changes in the vital activity of the organism. Even stimuli of short duration -- often transitory -- of the skin, muscles, or superficially located nerve branches lead to impairment of the normal activity of the organism. The changes engendered by pain stimuli are caused by the participation of the central nervous system and the involvement of the vegetative and the endocrine system in the reaction. The participation of these systems leads at the same time to comparatively rapid restoration of life activity after the cessation of the pain stimulus, provided the stimulation is not too strong and is of short duration.

In cases where the pain stimulus is very strong or where conditions are created for a continuous and prolonged stimulation, there is no restoration of functions to the initial, "pre-pain" level, and the changes in vital activity assume such proportions that a picture is created of an almost complete inhibition of vital functions, the syndrome of a so-called traumatic shock.

Traumatic shock develops most frequently after grave traumatic injuries.

A classic description of a traumatic shock syndrome, which develops under battle conditions, was made about one hundred years ago by N. I. Pirogov in his "Principles of General Military-Field Surgery." "The man whose arm or leg has been torn off, is lying in the first-aid station, numb, and immobile; he does not yell, does not complain, shows an interest in nothing and does not ask for anything; his body is cold, the pallor of the face resembles that of a corpse; his look is immobile and remote; his pulse is filiform, scarcely discernible under the finger, and often intermittent. The

numbed man does not answer questions addressed to him, or mumbles something to himself in a scarcely audible whisper; also, his breathing is hardly discernible. The wound and [adjoining] skin are almost completely insensitive; but, if the large nerve hanging from the wound is being stimulated, the patient will manifest some sign of sensation by a slight contraction of the facial muscles...."

We did not set ourselves the task of a detailed analysis of the problem of the etiology and pathogenesis of traumatic shock, nor of a systematic description of the changes in vital activity under conditions of shock. We must emphasize, however, that the nerve and pain factor is undoubtedly the basic etiological moment of the traumatic shock.

Any serious traumatic injury is naturally accompanied by sensations of pain. Under the effect of pain a strong stimulus may originate in the central nervous system, which generally spreads over the cortex -- often involving the sub-cortical areas of the brain -- and which characterizes the first, so-called erectile phase of the traumatic shock. At this stage the patient shows increased motor activity, accelerated cardiac rhythm, higher content of blood sugar, flooding of the organism by hormones, and a number of other phenomena which are usually observed in the case of strong, but not excessive, pain stimuli.

If by means of quickly employed measures the stream of pain impulses toward the central nervous system is checked, the shock development may be restricted to the first phase.

However, the rendering of first aid to a patient who had been subjected to a serious trauma (bone fracture, for instance), is often retarded to such an extent that conditions are created for the emergence of changes in the vital activity which assume the character of prolonged and progressive effects. As a result, at various periods, depending on the character, duration, and intensity of the pain stimulus, as well as the reactivity of the organism (at times very rapid), the first phase of shock is replaced by the second torpid phase of the traumatic shock. This phase -- the one described by N. I. Pirogov -- is characterized by disturbances of blood circulation, respiration, metabolism, trophic function, and the function of the glands of internal secretion. The circulatory and respiratory insufficiency leads to the development of hypoxia which further aggravates the course of shock.

The emergence of the second phase of shock is due to the flow of pain stimuli entering the already stimulated central nervous system from parts of the organism affected by trauma, and leads to the weakening and exhaustion of cellular elements of the cerebral cortex; after a while, a transliminal

inhibition emerges in the cortex which radiates into the sub-cortical region and into the lower areas of the central nervous system. Thus, the second phase of a traumatic shock is characterized by a state of deep inhibition.

The picture which emerges following a strong and prolonged pain stimulus is aggravated in trauma by the addition of another element -- the crushing of tissues. Loss of blood -- often considerable -- follows crushing. The loss itself of blood does not cause shock, but it aggravates the general state of the organism and creates a more favorable background for the origin of shock under the effect of the nerve and pain factor. The crushing of tissues in trauma creates conditions for the formation of toxic products, which, in turn, aggravates the course of shock. Some authors are of the opinion that loss of blood and toxemia are the basic etiological factors of traumatic shock.

Detailed clinical and experimental studies of traumatic shock (on animals) have shown, however, that pain is undoubtedly the primary etiological cause of traumatic shock, and that loss of blood and toxemia are only secondary, complicating factors (L. A. Orbeli, 1944; V. I. Popov, 1953).

Thus, traumatic shock must be regarded as one of the threatening effects of pain stimuli.

#### On the Mechanism of Realization of the Effects of Pain Stimuli

In discussing various aspects of vital activity of an animal organism we indicated that pain stimuli exert a marked effect on them, in changing the functional properties of the organism. However, only in isolated cases did we touch upon the problem of how these effects are realized and what the mechanism of the action of pain is on the organs and tissues of the organism.

Even in relatively recent times there was no answer to this question, no harmonious concept which would explain the entire complicated process of phenomena taking place upon the infliction of a pain stimulus on an animal or human being. We are indebted to our contemporary, the prominent American physiologist (now deceased), Walter Cannon, for the first attempt to formulate a theory of the realization of effects of pain stimuli.

Cannon (1914a, 1922, 1928, etc.), together with a number of his associates, demonstrated conclusively that emotional excitation (in which he also included pain) stimulates the sympathico-adrenal system and that the intensification of this is, in his opinion, responsible for the realization

of numerous reactions which are characteristic of pain!

Indeed, in the case of pain stimulation, as we had indicated in previous chapters, a number of changes occur which attest to the excitation of the sympathetic nervous system: higher blood pressure due to constriction of the blood vessels, acceleration of cardiac activity (the positive chronotropic effect), inhibition of the secretory activity of the gastric and pancreatic glands, decrease in the peristaltic activity of the intestines, retention of urine (reflex anuria), hyperglycemia, higher rate of blood coagulation, etc. According to Cannon, all these sympathetic effects are realized by means of adrenalin, the secretion of which increases under the effect of a pain stimulus. This was first demonstrated by Cannon in his joint work with Hoskins 1911-1912.

The secretion of adrenalin by the suprarenal glands is controlled by the sympathetic nervous system; the celiac nerves are the secretory nerves of the suprarenal glands (Biddle, 1897; Dreier, 1899; M. N. Cheboksarov, 1909, 1911, etc.).

It is now well known that the secretion of adrenalin by the suprarenals is not essential to the preservation of the life of the animal. Neither is the sympathetic nervous system vitally essential (Cannon, Newton, Bright, Minkin and Moore, 1929). Under normal laboratory conditions, completely desympathized animals showed no marked impairment of vital activity. However, when the conditions of existence placed increased demands on the animal organism (pain stimulus, muscular tension, emotional stimulus), the absence of the sympathetic nervous system and adrenalin secretion had a marked effect in manifesting a reduced capacity of the organism to adjust itself to the external environment. Cannon, having observed this as far back as 1914, pointed out the fact that the suprarenal cortex possesses an "emergency function"; later (1929), he extended this concept to the entire sympathico-adrenal system.

The Cannon concept impressed the investigators with its clarity, congruity, and experimental thoroughness, but, facts had already been established in the 20's which did not fit within the frame work of this concept, or even were directly contradictory to it.

Under the effect of pain stimuli, an increase of the secretory activity of other internal secretion glands besides the suprarenals was observed, and data were obtained which attested to the heightened activity of the sympathetic and parasympathetic nervous systems. Finally, it was shown that in pain stimulation there are changes in the physiological activity of the highest section of the central nervous

system -- the cortex of the cerebral hemispheres which regulates activities of the endocrine system and all other sections of the nervous system, including the sympathetic one.

In the laboratory of L. A. Orbeli, during studies of the process of reflex anuria under pain stimulus, data were obtained which demonstrated that one could not explain the observed anuria by the action of adrenalin alone; a conclusion was arrived at that "in addition to the possible and highly probable mechanism of adrenalin secretion, there exist some other mechanisms which cause this anuric picture" (L. A. Orbeli, 1938)

Further investigation of this problem showed, as we had pointed out in previous chapters, that in the case of pain stimulation there is an increase of the incretory activity of all endocrine glands, and that many effects of pain stimuli can be partly explained by the influence of the hormones.

L. A. Orbeli attached particular importance to the heightened incretory activity of the hypophysis under the effect of the pain stimulus. Indeed, when we trace the role of the hypophysis in its phylogenetic aspect, we observe its obvious relationship to the protective reactions: during the comparatively early stages of its development these are predominantly passive-protective reactions; in higher developed organisms they are actively protective and aggressive reactions (A. A. Danilov, 1941 b). Experimental data submitted by a number of co-workers of L. A. Orbeli (N. A. Galitskaya, 1938, 1941; A. A. Danilov, 1934, 1937, 1940, 1941a, 1941b; S. M. Dionesov, 1937, 1948a, 1948b; N. I. Mikhel'son, 1936, 1938, etc.), showed the participation of the posterior hypophyseal lobe-hormones in the realization of certain effects of pain stimuli.

The involvement of the hypophysis in the system of organs which react to a pain stimulus by increased activity has a reflex character via the sympathetic nervous system.

However, it is impossible to explain all the important changes in vital activity which we discussed in previous chapters solely by the participation of adrenalin and the hormones of the hypophysis, as well as by the hormones of other endocrine glands. There is no doubt that the nervous system also exerts direct influence.

In regard to the problem of the mechanism of regulation of the digestive apparatus upon pain stimulus, L. A. Orbeli (1941) pointed out that the considerable disturbances of this activity which had been observed by many investigators are explained "partly by direct reflex influences, partly by a summary intervention of a large number of hormonal agents". What has been said of the mechanism of regulation of the



digestive function also pertains to the regulation of other activities of the organism.

The changes in vital activity in response to pain stimuli can not be regarded as separate, isolated phenomena; they must be looked upon as a reaction of the entire organism. Therefore, it is natural that the nervous system and its higher section -- the cortex of the large hemispheres of the brain -- must play a basic role on these phenomena, as the leading factor of the integration of the organism. As we pointed out in previous chapters, the changes in vital activity occur not only in response to direct pain stimuli, but also in response to natural or artificial factors which are concomitant with pain stimulus, i.e., in a conditioned reflex manner. In other words, in the realization of pain reactions the cerebral cortex also plays its part.

Though the role of the nervous system in these reactions is conclusive, an attempt has been made recently to substantiate the participation of the humoral mechanism alone in the realization of reactions of an animal organism to extraordinary actions in which the pain stimulus is also included. We have in mind the concept of the Canadian endocrinologist Sel'ye.

According to Sel'ye (1950) as the effect on the organism of some non-specific extraordinary stimulus (consequently, a pain stimulus also) a "stress" is manifested under which an increased demand is placed on the systems which preserve the optimum state of the organism. Sel'ye differentiates three stages in the development of stress. The first stage, the "alarm reaction", is characterized by the mobilization of the protective factors of the organism, particularly the increased secretion of cortico-steroids by the suprarenal cortex, to which Sel'ye ascribes an exceptional role in the adaptation reactions of the organism under the conditions of stress. If the adaptation of the organism to the effect of an extraordinary stimulus has taken place, the secretion of cortico-steroids decreases and becomes normal; this is the "resistance stage". Nevertheless, if the stress proves to be too strong, and the suprarenal cortex is unable to ensure the adaptation of the organism to the stress factor, the third stage emerges -- the "exhaustion stage".

Thus, Sel'ye considers the cortico-steroid secretion to be the basic factor of the above-mentioned adaptation of the organism.

However, it is well known at present that under normal conditions the incretory activity of the suprarenal cortex is functionally dependent on the incretory activity of the anterior hypophyseal lobe. Sel'ye believes therefore, that the

"alarm" state is ensured by the adrenocorticotrophic hormone of the hypophysis (ACTH) and by the corticosteroids; hypophysis -- suprarenal cortex -- is consequently the basic mechanism of the mobilization of the protective forces of the organism in its fight against the sequels of excessive stimulation. The mobilization of the "adaptation hormones" and their adaptive action are effected via humoral paths. Though Sel'ye does not especially emphasize the pain stimulus as a factor which leads to the emergence of stress, it is nevertheless obvious that the pain stimulus, a chronic and prolonged one in particular, plays a considerable role in this respect.

Many investigators have recently demonstrated convincingly that the secretion of ACTH is regulated by the nervous system (I. A. Eskin, 1956). In addition, N. V. Mikhaylova showed that the ACTH secretion can proceed along a conditioned reflex path in response to the stress signal (I. A. Eskin, 1956).

Thus, the Sel'ye concept of the exclusive participation of two endocrine glands in the protective reaction of the organism to the effect of an excessive stimulus, can not satisfy us completely; it is, in our opinion, as imperfect as the Cannon concept. There is no doubt that, upon the action of an excessive stimulus such as pain, a reflex mobilization of many protective factors of the organism takes place, and that ACTH and corticosteroids are only part of their links. Mobilization represents a reaction of the organism as a whole and is fulfilled with the obligatory participation of the higher sections of the central nervous system, provided the organism is intact.

All the above-stated facts refer entirely, of course, to the reaction mechanisms of an animal organism to a pain stimulus, and to the mechanisms of the realization of the effect of these stimuli.

#### Biological Significance of the Reactions of the Organism to pain Stimulus

In the introductory chapter we refer to the various changes in vital activity which take place upon pain stimulation, thereby inducing a series of chain reflexes directed primarily to the reestablishment of the impaired equilibrium, which had been caused by the pain stimulus; these reflexes are what Rishe (1902) called the means of "consecutive defense," and I. P. Pavlov -- the "physiological measure" against disease.



As mentioned above, animals (and man) may react in two ways to a pain stimulus: either by an increase of vital activity, or by its almost complete inhibition. In the first type of reaction we encounter an increase of the muscular tone and capacity for work, acceleration of cardiac activity, increase of blood pressure, acceleration of respiration, inhibition of the secretion of urine and gastric juices, increased decomposition of glycogen in the liver and a higher content of blood sugar, inhibition of intestinal peristalsis, as well as a number of other phenomena. All these reactions represent characteristic effects of increased activity of the sympathetic nervous system and of the sympathomimetic agent -- adrenalin -- whose secretion by the cortical suprarenal substance is increased after the pain stimulus.

However, not only does the adrenalin secretion increase as a result of pain stimulus; there is also an increase, as we observed, of the secretion of hormones by other endocrine glands. The hormone of the thyroid -- thyroxin -- contributes to the increased use of oxygen by the tissues and increases the metabolic processes of the organ. The hormones of the suprarenal cortex and the anterior hypophyseal lobe are the most important factors in the adaptation of the organism to the noxious effects of the environment. The corticosteroids, in particular, help in maintaining the stability of the iron content of the organ, which is an essential condition of normal vital activity. The hormones of the posterior hypophyseal lobe participate particularly in the regulation of the water metabolism of the organism.

In taking into account the above-mentioned facts, let us visualize the most important general reaction of the animal to the pain-inflicting agents -- either the attack of the animal on this agent (usually a stronger animal), or the flight from it. This requires, first of all, an increase in muscular activity. A strenuously working muscle needs a large intake of oxygen and energy resources. Both are supplied by the blood. Greater intake is ensured by a number of factors: redistribution of the blood, caused by the dilatation of the muscular blood vessels with the simultaneous constriction of the vessels of the internal organs; increase and acceleration of the flow of blood resulting from the accelerated rate of the heart action; acceleration of respiration which permits more oxygen to enter the lungs and subsequently, the blood; increased sugar content of the blood, which is the basic energy material. The intensified intake of oxygen by the blood is ensured by the increased number of erythrocytes in the peripheral blood. As indicated earlier, the pain stimulus causes emptying of the blood depot, that of the spleen in the

first place, with the discharge of the deposited erythrocytes into the blood.

Under natural circumstances the pain stimulus is generally accompanied by damage to the integumenta, accompanied by bleeding; the blood coagulation rate is increased, thus protecting the organism from excessive bleeding.

Intense muscular activity originating from infliction of a pain stimulus on an animal (or man) leads to an increase of heat formation; overheating of the body is counteracted by the acceleration of respiration and dilatation of the cutaneous blood vessels and in man by an increased excretion of perspiration. All of these reactions are of a reflex character and occur regularly under the effect of a pain stimulus. In a conditioned pain stimulus these reactions ensure the preparedness of the protective and compensating mechanisms for action against the destructive agent.

Changes also take place in the central nervous system following a pain stimulus and thus ensure a timely reorganization of its functional state on the level of tasks which are required by the organism.

There are cases, however, where the pain stimulus does not cause an increased activity but, instead, a marked depression. This generally occurs when stimulation is excessive. This inhibiting reaction develops in the cerebral cortex and permits the cortical cell (having been exposed to excessive excitation under the effect of the pain stimulus) to relax; consequently, it is protected from threatened destruction or, at least, from being affected by excessively heavy work. "There is," said I. P. Pavlov (1930), "reason to believe that the cortical cell does not become deeply affected while the process of inhibition is taking place." Thus, cortical inhibition, having developed as the result of a strong pain stimulus, constitutes the "physiological measure" against the disease.

The protective role of inhibition is most clearly manifested when it originates following strong and prolonged stimuli. In such cases the inhibition assumes a diffuse character and involves the lower areas of the central nervous system as well as the cortex, thus inhibiting the entire activity of the organism. We encounter this condition in shock. "It is not impossible that in extensive injuries, which produce dangerous manifestations, the organism inhibits -- as if on purpose -- the activity of many other organs apparently with the intention of concentrating itself on protecting the threatened point, or of forestalling by means of a state of rest the destruction of organs exposed to abnormal and difficult conditions" (I. P. Pavlov).

All the above-mentioned reactions of the organism to pain stimuli have a reflex origin, and in a number of cases the presence of the reflex of the humoral, hormonal link is observed on the efferent path. This does not necessarily refute the fact that the basic mechanism in the realization of reactions to a pain stimulus is the nervous system, the role of which "fell out" in Sel'ye's concept. Thus, the changes in vital activity resulting from pain stimulation constitute, on the one hand, disturbances of vital activity and, on the other hand, the "physiological measure" against the sequelae of these disturbances.

The data cited in this book attest convincingly to the fact that pain stimuli, even mild and of short duration, cause definite, though brief, changes in vital activity in animals and man. As a rule, the changes which follow these stimuli are quickly obliterated, and the physiological activity of the organism is re-established on the previous "pre-pain" level. The completeness and intensity of restitution of normal activity following such stimuli depend on the state of the central nervous system.

However, where the pain stimulus assumes a prolonged, chronic character, a stable reorganization of the physiological activity takes place with the emergence of changes which can be regarded as pathological. In such cases, foci of stagnant excitation are formed in the cerebral cortex on the basis of the developed inhibition; these are prone to become recrudescence under the effect of various additional stimuli.

On the strength of this, measures which reduce or eliminate the painful sensations must be regarded not only as symptomatic, alleviating therapy but as pathogenetic, causative therapy as well, since in this case the possibility of the origin or further extension of disturbances of vital activity, which are caused by the presence of pain, is eliminated.

We are certain, therefore, that further study of the mechanism of changes of vital activity following pain stimuli (the effects of pain stimuli) will undoubtedly aid in finding successful methods to increase the resistance of the organism to pain stimuli, on the one hand, and to remove the sensations of pain entirely, on the other.

The task of this book is to facilitate this study.

END